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amino acids 581-635 of human dihydropyrimidine dehydrogenase of SEQ ID NO: 1, and instructions for detecting a G residue or an A residue in human dihydropyrimidine dehydrogenase genomic DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

27. (Amended) The kit of claim 26, wherein the kit further comprises a restriction endonuclease which cleaves a human dihydropyrimidine dehydrogenase genomic DNA only if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue.

28. (Amended) The kit of claim 27, wherein the restriction endonuclease cleaves a Mae II cleavage site.

REMARKS

I. Status of the Claims:

Claims 1-11, 15-17, and 20-28 are pending in the application and presented for examination. Claims 1-11, 15-17, and 20-28 are amended herein.

Claims 1-11, 15-17, and 20-28 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 8-10, 15-17, 20, 22, 24, 26, and 27 stand rejected under 35 U.S.C. § 112, first paragraph for an alleged lack of enablement.

Claims 10, 11, 15, and 24 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gonzalez et al. in view of Meinsma et al.

Applicants respectfully traverse these rejections below.

II. Amendments to the Claims:

The Amendments to the claims add no new subject matter.

Claims 1, 2, 7, and 16 as amended recite subject matter related to "an A residue" at the specified position This subject matter is found throughout the specification which teaches the substitution of the G residue by an A residue causes a splicing defect. See original claim 1 for support.

Claim 2 as amended no longer recites "which comprises" and now recites "to detect therein." The subject matter is supported in the original claim and in the specification at p. 8, line 7.

Claims 3, 8, 20, and 22 as amended no longer recite "hybridizes." They now recite "complementary to a subregion of" recitals. Support can be found for this subject matter at p. 8 first paragraph.

Claims 4, 5, 9, and 16 as amended no longer recite "the presence or absence of a G residue."

Claims 6 and 7 are also amended for purposes of clarity.

Claim 9 is further amended to correct an antecedent basis.

Claims 10, 11, 15, and 26 as amended no longer recite "binds to" and recite instead "complementary to a subregion of."

Claims 17, 21, 23, 25, 27, and 28 no longer recite "recognizes" and substitute therefore "cleaves." Support for these amendments is found in the previous versions of these claims and throughout the specification.

Other minor changes in the wordings of the claims accommodate the above amendments and further clarify their meaning.

The amendments to the claims therefore add no new subject matter.

III. Rejections for Indefiniteness under 35 U.S.C. §112, 2nd paragraph:

A. Response to rejections of claims 1-9, 17, 20-23, and 27 for lack of clarity relating to the recitals related to the residue at nucleotide 434 of SEQ ID NO: 1.

Claim 1 and its dependent claims 2-5 and 20-21 stand rejected for an alleged lack of clarity with respect to the recitation of "comprises a G residue at the position indicated as nucleotide 434 of SEQ ID NO:1" in claim 1. The Action alleges claims 1-5 and 20-21 are unclear as to the scope of polynucleotides encompassed by the claims in regards to the nucleotide sequence and length of the polynucleotide *comprising* nucleotide 434 of SEQ ID NO:1. The Action alleges that the claims could be interpreted as meaning any genomic or intronic sequence of human DPD genomic DNA comprising G. Applicants respectfully disagree and do not acquiesce to the position of the Action. However, in order to expedite prosecution of the application, Applicants have amended claim 1 to address the concern identified by the Examiner. Independent claim 1 has been amended to recite:

> 1. (Twice amended) A method of detecting a splicing defect in a human dihydropyrimidine dehydrogenase gene, comprising determining whether the residue of a human genomic DNA encoding the human dihydropyrimidine dehydrogenase gene at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining whether the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue, wherein said gene the substitution of the G residue with an A residue at said position causes a splicing defect in the human dihydropyrimidine dehydrogenase gene.

Independent claim 6 and its dependent claims 7-9 and 22-23 stand rejected for an alleged lack of clarity with respect to the recitation of "determining whether the genomic DNA comprises a G residue at the position indicated as nucleotide 434 of SEQ ID NO:1."

Applicants respectfully disagree and do not acquiesce to the position of the Action with respect to this recital. However, in order to expedite prosecution of the application, Applicants have amended claim 6 to address the concern identified by the Examiner. Claim 6 has been amended to recite:

> 6. (Twice amended) A method of screening human patients for sensitivity to 5-fluorouracil, comprising isolating a genomic

DNA from the patient and determining whether a G residue is the residue of the DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

Claim 17 and claim 27 were each alleged to be unclear with respect to the meaning of the recital "a sequence comprising a residue in human dihydropyrimidine dehydrogenase genomic DNA at the position indicated as nucleotide 434 of SEQ ID NO:1."

Applicants respectfully disagree and do not acquiesce to the position of the Action with respect to this recital. However, in order to expedite prosecution of the application, Applicants have amended claims 17 and 27 to address the concern identified by the Examiner. Claim 17 has been amended to recite:

17. (Twice Amended) The kit of claim 15, wherein the kit further comprises a restriction endonuclease which cleaves a human dihydropyrimidine dehydrogenase genomic DNA only if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue.

Claim 27 has been similarly amended and recites:

27. (Amended) The kit of claim 26, wherein the kit further comprises a restriction endonuclease which cleaves a human dihydropyrimidine dehydrogenase genomic DNA only if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue.

Applicants believe that claims 1-9, 17, 20-23, and 27 as amended are clear, and respectfully request that the above rejections of such claims under 35 U.S.C. §112, 2nd paragraph, be withdrawn.

B. Rejection of claims 4, 5, 9, 16 and 26 for alleged lack of clarity with respect to the recitals of "presence or absence of a G residue."

The Action alleged that "It is not clear whether the 'absence of a G residue' is meant to be interpreted as a substitution of a G with another nucleotide or if the G is deleted."

While Applicants respectfully disagree and do not acquiesce to the position of the Action with respect to any alleged ambiguity of this recital, Applicants have amended claims to delete the recital at issue.

C. Rejection of claim 17 (claim 25 dependent therefrom), 21, 23, 25, 27, and 28 for alleged indefiniteness with respect to the recitals of "recognizes."

Claims 17 and 27 stand rejected for the recital of "restriction endonuclease which recognizes a sequence." Claims 21, 23, 25, and 28 stand rejected for the recital of "restriction endonuclease recognizes a Mae II cleavage site." The Action considered the term "recognizes" to be unclear and suggested that applicants replace the term "recognizes" with "cleaves." While Applicants respectfully disagree and do not acquiesce to the position of the Action with respect to any alleged ambiguity of this recital, Applicants have nevertheless accepted the suggestion and amended the claims accordingly.

Applicants respectfully request that the above rejection of claims 17, 21, 23, 25, 27, and 28 be withdrawn.

D. Rejection of claims 3, 8, 10, 11, 15, 20, 24, and 26 for alleged indefiniteness in the recitation of "hybridizing" and "binds to."

The Action alleges that the recitals of "hybridizing" and "binds to" are unclear absent a statement of the conditions under which hybridization or binding is performed. Nucleic acids which will hybridize or bind under some conditions will not necessarily hybridize or bind under different conditions.

While Applicants respectfully disagree and do not acquiesce to the position of the Action with respect to any alleged ambiguity of these recitals, Applicants have amended the claims. These claims now recite "complementary" when referring to primers (e.g., a "primer is complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence" as in claim 24).

Applicants respectfully request that the above rejection of claims 3, 8, 10, 11, 15, 20, 24, and 26 be withdrawn.

IV. Claim Rejections – 35 U.S.C. § 112, First Paragraph:

A. The rejection of claims 1-4, 8-10, 15-17, 20, 22, 24, 26, and 27 for alleged lack of enablement.

The Action maintains the previous rejection of claims 1-4, 8-10, 15-17, 20, 22, 24, 26 and 27 for an alleged lack of enablement. The Action maintains the rejection on the following grounds:

> The specification teaches only a single representative species of human intronic DPD genomic DNAs comprising nucleotide 434 of SEQ ID NO:1, i.e., SEQ ID NO:1, three representative species of PCR primers as encompassed by the claims, i.e., SEQ ID NOs:2-5 and a single representative species of restriction endonucleases, i.e., MaeII. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the description of being a human intronic DPD genomic DNAs comprising nucleotide 434 of SEQ ID NO:1, a PCR primer as encompassed by the claims, or a restriction endonuclease. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

1. Enablement of the method claims 1-4, 8, 9, and 20-22.

The above rejection is grounded on an alleged lack of enablement with respect to three subject matter areas:

1. the disclosure of the human intronic DPD genomic DNAs;
2. the disclosure of the PCR primers; and
3. the disclosure of the restriction endonucleases

Applicants address each of these areas in turn.

2. The DPD genomic subject matter.

As a threshold matter, it is important to establish what the claims at issue recite and also what they do not recite. Claims 1-4, and 20-21 are drawn to methods of detecting a splicing defect. Claims 8, 9, and 22 are drawn to methods of screening human patients for sensitivity to

5-fluorouracil. The DPD genomic DNA sequences are not claimed themselves in those claims. Claim 1, for example, recites:

> 1. (Twice amended) A method of detecting a splicing defect in a human dihydropyrimidine dehydrogenase gene, comprising determining whether the residue of a human genomic DNA encoding the human dihydropyrimidine dehydrogenase gene at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining whether the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue, wherein said gene the substitution of the G residue with an A residue at said position causes a splicing defect in the human dihydropyrimidine dehydrogenase gene.

Claim 1 encompasses those DPD gene variants "wherein said gene substitution of the G residue with an A residue causes a splicing defect." This functional recital indicates only such genes wherein the specified mutation of a G with an A causes a splicing defect in an otherwise functional splicing region.

Applicants teach how to determine whether or not the residue at position 434 is a G residue or an A residue by use of sequence-specific endonucleases or genomic DNA sequence analysis. Such techniques are exemplified in the Examples and taught throughout the specification. The recital therefore provides only for subject matter reasonably related to the scope of enablement in the specification.

Whether the method would work for a given DPD genome variant would depend, for example, upon the PCR primer used and whether the primer was mismatched due to a mutation at the target site. For example, assuming random point mutations, the probability of the PCR primer being directed toward a mutation site and so fail to function as a primer would be quite low. **Indeed, the specification shows that the method works for quite diverse human populations (see p. 28, Table II).** Moreover, the DPD amino acid and DNA sequences between species are highly conserved (see Fig. 3 of U.S. Patent No. 5,856,454 to Gonzalez et al. (enclosed)). Thus, the *intra*species variation should be even less than the *inter*species variation. Moreover, if one primer targeting a variant sequence did not work, it would be relatively simple for one of ordinary skill to identify and screen other complementary primers based upon the disclosed SEQ ID NO: 1. According to the Action's discussion of the obviousness of the present

primers, and the related discussion below, such an experimentation could not be undue where the sequences are taught.

Even assuming that the proposed method would not work for all such human genomic DNA variants, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. (see MPEP §2164.08(b)). The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

3. The PCR Primer Subject Matter.

In rejecting the claims for lack of enablement with respect to the scope of the encompassed primers, the Action stated:

> Applicants have provided only a single species of a human genomic DPD sequence, i.e., SEQ ID NO:1, which is insufficient to describe the entire genus of human genomic DPD sequences. Therefore, because the structural information needed to generate the claimed primers and methods of use thereof is derived from the genomic sequence, applicants have not sufficiently described the genus of human genomic DPD sequences such that one of skill in the art could visualize the entire genus of primers.

Applicants respectfully point out that claim 3 recites a primer which is *complementary to a subregion* of a human dihydropyrimidine dehydrogenase genomic nucleotide sequence. For example, claim 3 recites:

> 3. (Twice amended) The method of claim 2, wherein the method comprises amplifying the genomic DNA with a primer complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence of SEQ ID NO: 1.

The teaching of one species of the gene sequence provides a corresponding multitude of subregions upon which the sequence of a complementary primer can be based. In a highly conserved gene, the possibility of variants with a different sequence in a particular subregion does not affect the operability of primers directed toward other subregions of the variant gene. A

set of as few as three primers drawn to different subregions of the nucleotide sequence could be reasonably expected to operate for the great majority of such variants. While it is always possible to contemplate some species for which any given method might not work, that is not the test of patentability as set forth in MPEP §2164.08(b).

The Action also stated that "the Applicants have disclosed only a 433 nucleic acid sequence 5' of position 434 and only a 427 nucleic acid sequence 3' to position 434 of SEQ ID NO:1. Therefore, it is impossible to visualize all primers that bind within 500 nucleotides of nucleotide 434 of SEQ ID NO:1 as recited in previous claims 3, 8, 10, and 15." Applicants have amended claim 3 to recite:

> ... a primer complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence of SEQ ID NO: 1.

Claim 8 is similarly amended herein.

4. The restriction endonuclease subject matter.

The Action recognizes that the subject matter of the Mae II restriction endonuclease is enabled. The Action rejects claims 4 and 9 under 35 U.S.C. § 112, first paragraph, on the grounds that the application allegedly "does not reasonably provide enablement for a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by digesting DNA with *any* restriction endonuclease or a kit comprising PCR primers and *any* restriction endonuclease that recognizes *any* sequence comprising nucleotide 434 of SEQ ID NO:1 (claims 17 and 27). The Action considers that screening for any restriction endonuclease to cleave a sequence comprising nucleotide 434 of SEQ ID NO:1 would involve undue experimentation.

Applicants respectfully disagree. One of ordinary skill merely has only to search the existing databases for endonucleases with the required specificity. For instance, Applicants searched the Promega web site according to the recognition sequence ACGT and **with no experimentation at all** found four different endonucleases which were perfect matches (see attached print out of the web site search).

Applicants therefore request that the above grounds for rejecting claims 1-4, 8, 9, and 20-22 be reconsidered and withdrawn.

5. Enablement of composition claims 10, 11, and kit claims 15-17, 24, 26 and 27.

a) PCR subject matter

In rejecting the claims for lack of enablement with respect to the scope of the encompassed primers, the Action stated:

> Applicants have provided only a single species of a human genomic DPD sequence, i.e., SEQ ID NO:1, which is insufficient to describe the entire genus of human genomic DPD sequences. Therefore, because the structural information needed to generate the claimed primers and methods of use thereof is derived from the genomic sequence, applicants have not sufficiently described the genus of human genomic DPD sequences such that one of skill in the art could visualize the entire genus of primers.

Applicants have amended independent claim 10 to recite:

> 10.(Twice amended) A composition comprising a PCR primer complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence of SEQ ID NO: 1.

Independent claims 15 and 26 have been similarly amended. The claimed primers are complementary to subregions of the disclosed sequence of SEQ NO: 1 and thus enabled.

The Action also pointed out that the Applicants have disclosed only a 433 nucleic acid sequence 5' of position 434 and only a 427 nucleic acid sequence 3' to position 434 of SEQ ID NO:1. Therefore, it is impossible to visualize all primers that bind within 500 nucleotides of nucleotide 434 of SEQ ID NO:1 as recited in previous independent claims 10 and 15. Applicants have amended claim 10 to recite:

> ... a PCR primer complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence of SEQ ID NO: 1.

Claim 15 has been similarly amended and does not recite non-disclosed subject matter.

The enablement of the endonuclease subject matter recited in claims 19 and 27 is as discussed above.

Applicants therefore respectfully request that the rejection of claims 10, 11, and kit claims 15-17, 24, 26 and 27 be reconsidered and withdrawn.

V. Claim Rejections – 35 U.S.C. §103(a):

A. Rejection of claims 10, 11, 15, and 24 under 35 U.S.C. § 103(a) as being unpatentable over Gonzalez et al. in view of Meinsma et al.

Amended claims 10, 11, 15 and 24 recite primers which are complementary to a subregion of human DPD *intronic* genomic DNA. In order to create such primers, the skilled artisan would need to know the sequence of the intronic DNA. As discussed in the previous Amendment, the intronic sequence of the DPD gene is not disclosed by Meinsma or Gonzalez, nor would the intronic sequence be obvious in light of Meinsma or Gonzalez. Neither Meinsma nor Gonzales provide a disclosure that would enable one of ordinary skill in the art to make the *complementary* primers of claims 10, 11, 15, or 24. They do not disclose these intronic sequences.

The Action alleges that Meinsma or Gonzalez would motivate and enable one of ordinary skill in the art to look for and find the subject intronic sequences. Assuming for the sake of argument that the allegation is true, it would be insufficient to support a finding of obviousness with respect to the subject primers. Even if a general method of determining the intronic DNA sequence was known, the specific sequence of the intronic DNA **can not** be obvious. MPEP §2141.09 (2100-148, bottom left column) and the courts require more. See *In re Deuel*, 51 F.3d 1552 at 1559, 34 U.S.P.Q.2d 1210 at 1215 (Fed. Cir. 1995) (**"A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search."** (emphasis added))

The existence of a general method for gene cloning and sequencing in the prior art and the motivation to sequence a particular gene is **not** sufficient to render obvious a particular DNA molecule. In the absence of the actual sequence of the introns flanking the 165 bp exon, the skilled artisan would have no way to make a primer *complementary* to that sequence. Applicants therefore request that the above rejection of claims 10, 11, 15, and 24 be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (925) 472-5000.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1-11, 15-17, and 20-28 have been amended as follows:

1. (Twice amended) A method of detecting a splicing defect in a human dihydropyrimidine dehydrogenase gene, comprising determining whether the residue of a human genomic DNA encoding the human dihydropyrimidine dehydrogenase gene comprises [a G residue] at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining whether the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue, wherein said gene the substitution of the G residue with an A residue at said position causes a splicing defect in the human dihydropyrimidine dehydrogenase gene.

2. (Twice amended) The method of claim 1, wherein the method comprises the step of amplifying human intronic dihydropyrimidine dehydrogenase genomic DNA to detect therein [which comprises] a G residue or an A residue at the position indicated as nucleotide 434 of SEQ ID NO: 1.

3. (Twice amended) The method of claim 2, wherein the method comprises amplifying the genomic DNA with a primer complementary to a subregion of [which hybridizes to a] the human dihydropyrimidine dehydrogenase genomic nucleotide sequence [located within 500 nucleotides of the position indicated as nucleotide 434] of SEQ ID NO: 1.

4. (Twice amended) The method of claim 2, wherein the [presence or absence of the G residue is detected using an] detecting is by digestion of the amplified DNA with a restriction endonuclease.

5. (Twice amended) The method of claim 1, wherein the [presence or absence of the G residue is detected using an] determining is by oligonucleotide array.

6. (Twice amended) A method of screening human patients for sensitivity to 5-fluorouracil, comprising isolating a genomic DNA from the patient and determining whether

[the genomic DNA comprises] a G residue is the residue of the DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

7. (Twice amended) The method of claim 6, wherein the method comprises the step of amplifying human intronic dihydropyrimidine dehydrogenase genomic DNA from the patient [which comprises a] and determining if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue.

8. (Twice amended) The method of claim 7, wherein the method comprises amplifying the genomic DNA with a primer [which hybridizes to a] complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence [located within 500 nucleotides of the position indicated as nucleotide 434] of SEQ ID NO: 1.

9. (Twice amended) The method of claim 7, wherein the [presence or absence of the G residue is detected by] determining is by digestion of the amplified DNA with a restriction endonuclease.

10. (Twice amended) A composition comprising a PCR primer [which binds to] complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence [located within 500 nucleotides of the position indicated as nucleotide 434] of SEQ ID NO: 1.

11. (Twice amended) The composition of claim 10, wherein the PCR primer [binds to] is complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

15. (Twice amended) A kit comprising a container, a first PCR primer [which binds to] complementary to a subregion of DNA 3' of a splice site in the human genomic DNA for an exon encoding amino acids 581-635 of human dihydropyrimidine dehydrogenase, and a second PCR primer [which binds to] complementary to a subregion of DNA 5' of a splice site in

the human genomic DNA for an exon encoding amino acids 581-635 of human dihydropyrimidine dehydrogenase, wherein at least one of the first or second PCR primers [binds to] is complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence [located within 500 nucleotides of the position indicated as nucleotide 434] of SEQ ID NO: 1.

16. (Twice amended) The kit of claim 15, wherein the kit further comprises instructions for [the detection of] detecting a G residue or an A residue [the presence or absence of a G residue] in human dihydropyrimidine dehydrogenase genomic DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

17. (Twice Amended) The kit of claim 15, wherein the kit further comprises a restriction endonuclease which cleaves [recognizes a sequence comprising a residue in] a human dihydropyrimidine dehydrogenase genomic DNA only if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue.

20. (Amended) The method of claim 2, wherein the method comprises amplifying the genomic DNA with a primer [which hybridizes to] complementary to a subregion of a human dihydropyrimidine dehydrogenase genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

21. (Amended) The method of claim 4, wherein the restriction endonuclease [recognizes] cleaves a Mae II cleavage site.

22. (Amended) The method of claim 8, wherein the method comprises amplifying the genomic DNA with a primer which is complementary [hybridizes] to a subregion of a human dihydropyrimidine dehydrogenase genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

23. (Amended) The method of claim 9, wherein the restriction endonuclease [recognizes] cleaves a Mae II cleavage site.

24. (Amended) The kit of claim 15, wherein at least one of the first or second PCR primers is complementary [binds] to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

25. (Amended) The kit of claim 17, wherein the restriction endonuclease [recognizes] cleaves a Mae II cleavage site.

26. (Amended) A kit comprising a container, a first PCR primer which [binds to] is complementary to a subregion of the DNA sequence of SEQ ID NO: 1 which is 3' of a splice site in the human genomic DNA for an exon encoding amino acids 581-635 of the human dihydropyrimidine dehydrogenase, a second PCR primer which [binds to] is complementary to a subregion of the DNA of SEQ ID NO: 1 5' of a splice site in the human genomic DNA for an exon encoding amino acids 581-635 of human dihydropyrimidine dehydrogenase of SEQ ID NO: 1, and instructions for [the detection of the presence or absence of] detecting a G residue or an A residue in human dihydropyrimidine dehydrogenase genomic DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

27. (Amended) The kit of claim 26, wherein the kit further comprises a restriction endonuclease which [recognizes] cleaves [a sequence comprising a residue in] a human dihydropyrimidine dehydrogenase genomic DNA only if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue.

28. (Amended) The kit of claim 27, wherein the restriction endonuclease [recognizes] cleaves a Mae II cleavage site.

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APPENDIX I

PENDING CLAIMS FOLLOWING ENTRY OF THIS AMENDMENT

1. (Twice amended) A method of detecting a splicing defect in a human dihydropyrimidine dehydrogenase gene, comprising determining whether the residue of a human genomic DNA encoding the human dihydropyrimidine dehydrogenase gene at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining whether the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue, wherein said gene the substitution of the G residue with an A residue at said position causes a splicing defect in the human dihydropyrimidine dehydrogenase gene.

2. (Twice amended) The method of claim 1, wherein the method comprises the step of amplifying human intronic dihydropyrimidine dehydrogenase genomic DNA to detect therein a G residue or an A residue at the position indicated as nucleotide 434 of SEQ ID NO: 1.

3. (Twice amended) The method of claim 2, wherein the method comprises amplifying the genomic DNA with a primer complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence of SEQ ID NO: 1.

4. (Twice amended) The method of claim 2, wherein the detecting is by digestion of the amplified DNA with a restriction endonuclease.

5. (Twice amended) The method of claim 1, wherein the determining is by oligonucleotide array.

6. (Twice amended) A method of screening human patients for sensitivity to 5-fluorouracil, comprising isolating a genomic DNA from the patient and determining whether a G residue is the residue of the DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

7. (Twice amended) The method of claim 6, wherein the method comprises the step of amplifying human intronic dihydropyrimidine dehydrogenase genomic DNA from the

patient and determining if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue or determining if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is an A residue.

8. (Twice amended) The method of claim 7, wherein the method comprises amplifying the genomic DNA with a primer complementary to a subregion of the human dihydropyrimidine dehydrogenase genomic nucleotide sequence of SEQ ID NO: 1.

9. (Twice amended) The method of claim 7, wherein the determining is by digestion of the amplified DNA with a restriction endonuclease.

10. (Twice amended) A composition comprising a PCR primer complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence of SEQ ID NO: 1.

11. (Twice amended) The composition of claim 10, wherein the PCR primer is complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

15. (Twice amended) A kit comprising a container, a first PCR primer complementary to a subregion of DNA 3' of a splice site in the human genomic DNA for an exon encoding amino acids 581-635 of human dihydropyrimidine dehydrogenase, and a second PCR primer complementary to a subregion of DNA 5' of a splice site in the human genomic DNA for an exon encoding amino acids 581-635 of human dihydropyrimidine dehydrogenase, wherein at least one of the first or second PCR primers is complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence of SEQ ID NO: 1.

16. (Twice amended) The kit of claim 15, wherein the kit further comprises instructions for detecting a G residue or an A residue in human dihydropyrimidine dehydrogenase genomic DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

17. (Twice Amended) The kit of claim 15, wherein the kit further comprises a restriction endonuclease which cleaves a human dihydropyrimidine dehydrogenase genomic DNA only if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue.

20. (Amended) The method of claim 2, wherein the method comprises amplifying the genomic DNA with a primer complementary to a subregion of a human dihydropyrimidine dehydrogenase genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

21. (Amended) The method of claim 4, wherein the restriction endonuclease cleaves a Mae II cleavage site.

22. (Amended) The method of claim 8, wherein the method comprises amplifying the genomic DNA with a primer which is complementary to a subregion of a human dihydropyrimidine dehydrogenase genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

23. (Amended) The method of claim 9, wherein the restriction endonuclease cleaves a Mae II cleavage site.

24. (Amended) The kit of claim 15, wherein at least one of the first or second PCR primers is complementary to a subregion of a human dihydropyrimidine dehydrogenase intronic genomic nucleotide sequence located within 100 nucleotides of the position indicated as nucleotide 434 of SEQ ID NO: 1.

25. (Amended) 25. The kit of claim 17, wherein the restriction endonuclease cleaves a Mae II cleavage site.

26. (Amended) A kit comprising a container, a first PCR primer which is complementary to a subregion of the DNA sequence of SEQ ID NO: 1 which is 3' of a splice site in the human genomic DNA for an exon encoding amino acids 581-635 of the human

dihydropyrimidine dehydrogenase, a second PCR primer which is complementary to a subregion of DNA of SEQ ID NO: 1 5' of a splice site in the human genomic DNA for an exon encoding amino acids 581-635 of human dihydropyrimidine dehydrogenase of SEQ ID NO: 1, and instructions for detecting a G residue or an A residue in human dihydropyrimidine dehydrogenase genomic DNA at the position indicated as nucleotide 434 of SEQ ID NO: 1.

27. (Amended) The kit of claim 26, wherein the kit further comprises a restriction endonuclease which cleaves a human dihydropyrimidine dehydrogenase genomic DNA only if the residue at the position indicated as nucleotide 434 of SEQ ID NO: 1 is a G residue.

28. (Amended) The kit of claim 27, wherein the restriction endonuclease cleaves a Mae II cleavage site.